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Analysis of Preincisional and Postincisional Treatment with Alpha2-Adrenoreceptor Agonist Clonidine Regarding Analgesic Consumption and Hemodynamic Stability in Surgical Patients

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ABSTRACT

Preemptive analgesia aims to prevent the sensitization of central nervous system, hence the development of pathologic pain after tissular injury. The aim of the study was to assess the effect of preincisional clonidine treatment on analgesic consumption and hemodynamic stability compared to clonidine administered at the end of the operation and control group. Ninety-one patients undergoing elective colorectal surgery were randomly assigned to four groups: peroral clonidine before operation, epidural clonidine before operation, epidural clonidine at the end of operation, and epidural saline before operation as a control group. After the operation, patient-controlled analgesia with epidural morphine was instituted. Analgesic consumption, blood pressure and heart rate were obtained at 1, 2, 6 and 24 h postoperatively, and the cumulative consumption of analgesics was assessed at the end of the study period. Significant differences ($p<0.05$) in postoperative systolic blood pressure, with highest hemodynamic stability was observed at 1 h and 6 h in the group of patients administered epidural clonidine before operation. In this group of patients we found significant reduction in analgesic consumption during the study period ($p<0.05$), compared to other groups. The cumulative consumption of analgesics assessed at the end of the study period was significantly reduced ($p<0.05$) in the group of patients administered epidural clonidine before operation (8.40±3.74, respectively) as compared with the peroral clonidine before operation (16.79±5.75, respectively), epidural clonidine at the end of the operation (11.11±4.24, respectively) and control group of patients (18.00 ±6.45, respectively). Preincisional administration of epidural clonidine was associated with a significantly lower analgesic use, lower cumulative analgesic consumption and greater hemodynamic stability, in comparison with other groups.

Key words: *epidural analgesia, patient-controlled analgesia, clonidine*

Introduction

As a broader definition of preemptive analgesia, preventive analgesia aims to prevent the sensitization of central nervous system, hence the development of pathologic pain after tissular injury. Objective evaluation of postoperative pain such as wound hyperalgesia and analgesic consumption is necessary, in order to demonstrate benefit from preventive treatment[1–3].

Study results in the field of preemptive analgesia are not always comparable; they vary according to different study design and type of performed surgery. To provide definitive evidence for a preemptive analgesic effect the postincisional treatment group should be a part of the study design. Otherwise, the possibility that the results were due to persistent effects of the analgesic regimen

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rather than a true preemptive effect remains. Also, Katz et al. highlight the importance of including a standard treatment control group to avoid problems of interpretation that may arise when two-group studies (preincisional vs. postincisional) fail to find the anticipated effects[4,5].

The alpha2-adrenoreceptor agonists have several beneficial actions during the perioperative period. They exert a central sympatholytic action, improving hemodynamic stability in response to endotracheal intubation and surgical stress, reducing the opioid requirements and causing sedation, anxiolysis and analgesia. Stimulation of alpha2-adrenoreceptors of neurones in the nucleus tractus solitarius, augments the inhibition by this nucleus of the sympathetic neurones of the medulla. In this way, they reduce the tonic activity of the baroreflex, decreasing arterial pressure and causing bradycardia. In both healthy volunteers and patients, alpha2-adrenoreceptor agonists decrease plasma catecholamine levels. Furthermore, they may offer benefits in the prophylaxis and treatment of perioperative myocardial ischaemia by prevention of hypertension and tachycardia, decrease the incidence of shivering and reduce tissue oxygen consumption[6].

Clonidine inhibits transmission of nociceptive stimuli in the dorsal horn of the spinal cord, acting on the inhibitory descending pathways, modulates the release of serotonin and norepinephrine, and blocks the transmission of pain[7]. Study of Kita et al. demonstrated the alpha2-adrenoreceptors in the region above the mesencephalon to contribute significantly to clonidine analgesia and hemodynamic stabilizing effects[8].

Kawasaki et al. reported that clonidine inhibits transmission to the gelatinous substance neurons through the activation of alpha2-adrenoceptors as a part of the inhibitory modulation of pain sensation[9].

The aim of our study was to assess the effect of preincisional clonidine treatment on analgesic consumption and hemodynamic stability. The study was so designed as to compare the preincisional and postincisional treatment, and then both with the control group.

Materials and Methods

The investigation was carried out in the double-blinded manner, with due approval from the institution Ethics Committee and an informed consent from all study subjects. Ninety-one patients undergoing colorectal resection surgery were randomly assigned to four groups: peroral clonidine before operation, epidural clonidine before operation, epidural clonidine at the end of operation, and epidural saline before operation as a control group.

Exclusion criterion was the operation time exceeding six hours. According to the perioperative risk of anesthesia and operation, study patients were classified as ASA (American Society of Anesthesiologists) physical status I or II. There were no significant differences among groups of patients in age, sex and body weight. Surgical procedure were similar, and included colonic and rectal resection.

Before the operation, a 20 G epidural catheter was inserted throught the 18 G Tuohy needle at the Th10-L1 level. Correct positioning was tested using 2 mL of 2% lidocaine.

Clonidine (Catapres®, Boehringer Ingelheim) was administered in a dose of 5 μg/kg (peroral or epidural), 45 min prior to skin incision or at the end of operation. Epidural clonidine was administered as a bolus, diluted in 20 mL of isotonic saline. Control group received bolus of epidural saline. Each group in our study received identical anesthesia using midazolam (0.15 mg/kg), fentanyl (2 μg/kg) and rocuronium (0.6 mg/kg) to facilitate endotracheal intubation, and nitrous oxide 50% in oxygen, sevoflurane and bolus of rocuronium for maintenance. Therefore, anesthetics affected all groups equivalently. Upon the pain complaint, all patients received identical analgesia with boluses of epidural morphine 0.06 mg/kg diluted in 20 mL of isotonic saline. Analgesic consumption, blood pressure and heart rate were obtained at 1, 2, 6 and 24 h postoperatively. In addition, the cumulative use of analgesics was assessed at the end of the study period.

Differences in blood pressure, heart rate and cumulative analgesics consumption were evaluated using the one-way analysis of variance (ANOVA). Statistical significance was set at $p<0.05$. Results were expressed as X±SD. Quantitative differences in analgesic consumption were evaluated with χ^2 test, and if needed Fisher's Exact test.

Results

Significant differences in postoperative systolic blood pressure, with highest reported hemodynamic stability

TABLE 1
SISTOLIC BLOOD PRESSURE

Sistolic blood pressure /mmHg/	Peroral clonidine before operation	Epidural clonidine before operation	Epidural clonidine at the end of operation	Control group	p
1 h	141.21±18.92	130.08±18.67	136.96±15.63	147.76±19.79	0.00887
2 h	144.00±18.61	134.52±20.23	136.00±18.17	135.44±15.74	0.43359
6 h	151,07±16.78	135.72±17.16	149.81±16.78	144.60±19.93	0.01977
24 h	140.50±23.79	135.44±14.06	146.33±18.62	140.72±16.75	0.19304

TABLE 2
HEART RATE

Heart rate /min/	Peroral clonidine before operation	Epidural clonidine before operation	Epidural clonidine at the end of operation	Control group	p
1 h	86.36±2.51	76.16±12.28	71.85±9.89	86.20±16.73	0.00026
2 h	89.14±12.22	78.40±14.37	72.59±9.83	85.64±14.22	0.00025
6 h	95.93±15.93	78.52±13.40	82.19±11.32	92.68±13.61	0.00008
24 h	94.43±15.99	75.20±11.75	81.26±10.19	89.40±15.77	0.00006

was observed at 1 h and 6 h in the group of patients administered epidural clonidine before operation (130.08± 18.67 and 135.72±17.16, respectively) as compared with the peroral clonidine before operation (141.21±18.92 and 151.07±16.78, respectively), epidural clonidine at the end of the operation (136.96±15.63 and 149.81±16.78, respectively) and control group of patients (147.76±19.79 and 144.60±19.93, respectively). During the investigation period in epidural clonidine before operation group, the widest range between the measured values of systolic blood pressure was within 5% (Table 1). There was no significant difference in diastolic blood pressure values among the groups. Comparison of heart rate yielded significant differences among the groups of patients. In the group of patients administered epidural clonidine before the operation heart rate values were within the normal limits during investigation period, as compared with other groups (in peroral clonidine before the operation and control group heart rate were out of normal limits at 1, 2, 6 and 24 h, and in the epidural clonidine at the end of the operation at 6 h and 24 h) (Table 2). There was significant difference in analgesic consumption among the

TABLE 3
ANALGESIC CONSUMPTION AT 1 H

Group	Patients	1 h		Total
		No analgesisc	Analgesics	
Peroral clonidine before operation	N	9	5	14
	(%)	64.3%	35.7%	100%
Epidural clonidine before operation	N	22	3	25
	(%)	88.0%	12.0%	100%
Epidural clonidine at the end of operation	N	27	–	27
	(%)	100.0%	–	100%
Control group	N	6	19	25
	(%)	24.0%	76.0%	100%
Total	N	64	27	91
	(%)	70.3%	29.7%	100%

Fischer's Exact Test $p<0.001$; $\chi^2=41.092$; $p=0.0000$

TABLE 4
ANALGESIC CONSUMPTION AT 2 H

Group	Patients	2 h		Total
		No analgesisc	Analgesics	
Peroral clonidine before operation	N	8	6	14
	(%)	57.1%	42.9%	100%
Epidural clonidine before operation	N	17	8	25
	(%)	68%	32%	100%
Epidural clonidine at the end of operation	N	26	1	27
	(%)	96.3%	3.7%	100%
Control group	N	7	18	25
	(%)	28.0%	72.0%	100%
Total	N	58	33	91
	(%)	63.7%	36.3%	100%

Fischer's Exact Test $p<0.001$; $\chi^2=21.991$; $p=0.0001$

TABLE 5
ANALGESIC CONSUMPTION AT 6 H

Group	Patients	6 h		Total
		No analgesisc	Analgesics	
Peroral clonidine before operation	N	2	12	14
	(%)	14.3%	85.7%	100%
Epidural clonidine before operation	N	14	11	25
	(%)	56.0%	44.0%	100%
Epidural clonidine at the end of operation	N	1	26	27
	(%)	3.7%	96.3%	100%
Control group	N	4	21	25
	(%)	16.0%	84.0%	100%
Total	N	21	70	91
	(%)	23.1%	76.9%	100%

Fischer's Exact Test $p<0.001$; $\chi^2=22.289$; $p=0.0001$

TABLE 6
ANALGESIC CONSUMPTION AT 24 H

Group	Patients	24 h		Total
		No analgesisc	Analgesics	
Peroral clonidine before operation	N	4	10	14
	(%)	28.6%	71.4%	100%
Epidural clonidine before operation	N	12	13	25
	(%)	48.0%	52.0%	100%
Epidural clonidine at the end of operation	N	7	20	27
	(%)	25.9%	74.1%	100%
Control group	N	3	22	25
	(%)	12.0%	88.0%	100%
Total	N	26	65	91
	(%)	28.6%	71.4%	100%

Fischer's Exact Test $p<0.05$; $\chi^2=8.081$; $p=0.0444$

groups. Administration of epidural clonidine before the operation produced significant reduction in analgesic consumption during the study, as compared to other three groups. In the group of patients administered epidural clonidine at the end of the operation, a very low analgesic consumption was observed at 1 h and 2 h (0% and 3.7%, respectively), and a significant increase at 6 h and 24 h (96.3% and 74.1%, respectively) (Tables 3–6).

The cumulative consumption of analgesics assessed at the end of the study period was significantly reduced ($p<0.05$) in the group of patients administered epidural clonidine before operation (8.40±3.74, respectively) as compared with the peroral clonidine before operation (16.79±5.75, respectively), epidural clonidine at the end of the operation (11.11±4.24, respectively) and control group (18.00±6.45, respectively).

Discussion

Studies comparing preincisional and postincisional treatment in major digestive surgery patients were predominantly using local anesthetics and opioids. Clonidine was usually used in combination with these analgesics. When preemptive treatment was instituted using epidural and intrathecal route, it resulted in better postoperative pain control and lower analgesic consumption compared with intravenous and peroral administration.

In the study of Lavand'homme et al. intraoperative intravenous and epidural treatment with a combination of local anesthetics, opioids and clonidine were compared. They found that epidural analgesia provided effective preventive analgesia after major abdominal surgery[10]. This multireceptor approach failed to exert a clinically relevant effect when analgesics were used intravenously, as in study of Holthusen et al. They used intravenous preincisional clonidine with morphine and ketamine in patients undergoing transperitoneal tumor nephrectomy[11]. Study of preincisional treatment with clonidine as a sole analgesic for abdominal surgery patients by De Kock et al. reported significantly lower morphine requirements in clonidine group. Patients received preincisional clonidine or bupivacaine, without compar-

ing the analgesic effect with a postincisional group[12]. Another study, by Wu et al., reported that preincisional epidural clonidine treatment compared with control group (preincisional saline) produced longer patient controlled epidural analgesia (PCEA) trigger times, less morphine consumption and reduced perioperative cytokine response[13].

In our study, clonidine was administered by peroral and epidural route. Epidural clonidine analgesia begins within 30 min and lasts for 4–5 h. The group of patients with preoperative epidural clonidine administration showed continuously reduced analgesic consumption, as a result of reduced incidence of postoperative hyperalgesia. Hemodynamic stability reported in this group support these findings. Our results of improved preincisional clonidine analgesia could be compared with those reported by De Kock et al. We believe that it was the result of the clonidine central blocking the transmission of nociceptive stimuli along descending pathways. The cumulative analgesic consumption was not reduced in peroral clonidine before the operation group compared with epidural clonidine in the same dose. Further investigation with high doses of peroral clonidine will be needed for definitive recommendation regarding the effect of peroral clonidine on analgesic consumption and hemodynamic stability.

Patients who received clonidine at the end of operation showed very low analgesic consumption at 1 h and 2 h, when the concentration of clonidine was very high, followed by a significant increase at 6 h and 24 h. Thus, postincisional treatment provided short-lasting analgesia and secondary hyperalgesia.

Conclusion

In conclusion, preincisional administration of epidural clonidine was associated with a significantly lower analgesic use, lower cumulative analgesic consumption and greater hemodynamic stability, in comparison with preincisional administration of peroral clonidine, postincisional administration of epidural clonidine and the control group of patients. Improved preemptive analgesia may be achieved by epidural clonidine administration.

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ANALIZA PRIJEOPERACIJSKE I POSLIJEOPERACIJSKE PRIMJENE ALFA2-ADRENERGIČKOG AGONISTA KLONIDINA OBZIROM NA POTROŠNJU ANALGETIKA I HEMODINAMSKU STABILNOST U KIRURŠKIH BOLESNIKA

SAŽETAK

Osnova preemptivne analgezije je sprječavanje nastanka senzitizacije središnjeg živčanog sustava i posljedičnog razvoja patološke boli uslijed tkivne ozljede. Cilj ove studije bila je usporedba učinka prijeoperacijske primjene klonidina na

potrošnju analgetika i hemodinamsku stabilnost bolesnika u odnosu na primjenu klonidina na kraju operacije i kontrolnu skupinu. Uzorak od ukupno 91 bolesnika, predviđenih za operacijski zahvat u kolorektalnoj kirurgiji, metodom randomizacije podijeljen je u četiri skupine: klonidin per os prije operacije, epiduralni klonidin prije operacije, epiduralni klonidin na kraju operacije i kontrolna skupina. Nakon operacijskog zahvata, na pojavu osjeta boli svi ispitanici su primili analgetik morfin. Parametri krvnog tlaka, pulsa i učestalosti potrošnje analgetika proučavani su u vremenskom slijedu 1., 2., 6. i 24. sata od operacijskog zahvata, a ukupna potrošnja analgetika na završetku ispitivanja. Značajne razlike ($p<0,05$) u vrijednostima sistoličkog krvnog tlaka, uz najveću hemodinamsku stabilnost bolesnika dokazane su u skupini s klonidinom primjenjenim epiduralno prije operacije u 1. i 6. satu ispitivanja. U toj skupini bolesnika nađeno je značajno smanjenje primjene analgetika tijekom ispitivanja ($p<0,05$), u usporedbi s ostalim skupinama. Ukupna potrošnja analgetika na završetku ispitivanja bila je značajno manja ($p<0,05$) u skupini bolesnika s klonidinom primjenjenim epiduralno prije operacije (8,40±3,74), u usporedbi s klonidinom primjenjenim per os prije operacije (16,79± 5,75), klonidinom epiduralno na kraju operacije (11,11±4,24) i kontrolnom skupinom bolesnika (18,00±6,45). Zaključujemo da je prijeoperacijska epiduralna primjena klonidina povezana s smanjenom učestalosti primjene analgetika, smanjenom ukupnom potrošnjom analgetika i većom hemodinamskom stabilnosti, u usporedbi s ostalim ispitivanim skupinama.